MED MEDIZINISCHE FAKULTÄT

Forschungsbericht 2019

Institut für Experimentelle Innere Medizin

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1. LEITUNG

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2. HOCHSCHULLEHRER/INNEN

Univ.-Prof. Dr. rer. nat. habil. Michael Naumann

3. FORSCHUNGSPROFIL

- NF-kB, Pathogen-Infektion
- NF-kB, angeborene Immunantwort und Entzündung
- NF-kB, Zellüberleben und Krebsentstehung
- Ubiquitin-Proteasom System
- COP9 Signalosom und Adipogenese
- Biomolekulare Modellierung / Wirkstoffforschung
- Massenspektrometrie

4. FORSCHUNGSPROJEKTE

Projektleitung: Prof. Dr. Michael Naumann
Förderer: Deutsche Forschungsgemeinschaft (DFG) - 01.10.2018 - 31.03.2023

Maladaptive processes across physiological barriers in chronic diseases

Graduiertenkollge 2408
Chronische Erkrankungen stellen eine zunehmende gesundheitspolitische Herausforderung dar. Zelluläre Maladaptationen und die fehlgeleitete Zell-Zellkommunikation an physiologischen Barrieren sind mechanistische Aspekte von zentraler Bedeutung bei chronischen Erkrankungen wie Atherosklerose oder chronische Erkrankungen der Niere, der Haut, oder des Gastrointestinaltrakts. Physiologische Grenzflächen werden durch hoch spezialisierte Zellen, z.B. **Endothelzellen** oder **Epithelzellen**, definiert. Störungen in der Regulation und Funktion dieser Grenzflächen führen zu einem pathophysiologischen Mikromilieu, charakterisiert z.B. durch ein spezifisches Sekretom sowie der Aktivierung lokaler Zellen und/oder Rekrutierung von Entzündungszellen. Von besonderer Bedeutung bei chronischen Erkrankungen ist die **Perpetuierung maladaptiver Prozesse,** die auf **posttranslationalen Proteinmodifikationen** beruhen. Das Verständnis molekularer Veränderungen, die maladaptiven Krankheitsprozessen an physiologischen Grenzflächen zugrunde liegen, ist derzeit noch sehr limitiert. Innerhalb des **GRKs** beabsichtigen wir Krankheit-auslösende maladaptive Prozesse an **endothelialen und epithelialen Grenzflächen** zu erforschen.

Projektleitung: Prof. Dr. Michael Naumann
Förderer: Deutsche Forschungsgemeinschaft (DFG) - 01.01.2018 - 31.12.2021

Helicobacter pylori type IV secretion system-directed membrane-proximal NF-kB signaling

In the stomach, chronic infection with the pathogen *Helicobacter pylori* represents a risk factor for the development of chronic inflammation, which is a potent promoter for metaplasia, dysplasia and cancer development. Colonization of gastric epithelial cells by *H. pylori* induces fast activation of the proinflammatory and survival factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). Activation of canonical NF-kB is strictly induced only by *H. pylori* strains carrying a cag pathogenicity island (*cag*PAI), which encodes a type IV secretion system (T4SS). Further, it has been suggested that *Helicobacter* outer membrane protein (HopQ), could contribute to NF-kB activation. The detailed mechanism of T4SS-dependent activation of membrane-proximal NF-kB activation is unresolved so far. Regarding the molecular mechanism responsible for canonical NF- B activation and inflammation in infected gastric cancer cell lines we defined as crucial elements the TAK1/TAB complex and the E3 ubiquitin ligase TRAF6, which are situated upstream of the NF-kB inhibitor B kinase (IKK) complex. To identify *H. pylori*-induced proximal NF-kB signaling molecules which regulate substrate ubiquitinylation, we performed siRNA screens with human ON-TARGETplus siRNA libraries which selectively knockdown F-box and SOCS-box E3 enzymes, or RING-finger and RING-finger-like E3 single protein ligases. Some identified molecules contribute to NF-kB regulation, e.g. Ankyrin repeat and SOCS box protein 3 (ASB3), the Tripartite motif protein containing 28 (TRIM 28) and the ubiquitin-editing enzyme A20. Interestingly, we assigned that *H. pylori*-induced A20 terminates NF-kB activation, but also attenuates host apoptotic cell death. The overall aim of this project is to decipher the complex regulation of the membrane-proximal signal transmission leading to the activation of canonical NF-kB during *H. pylori* infection. In detail, we plan to elucidate bacterial T4SS components and Hop-protein adhesins, and their interplay with eukaryotic surface factors (receptors) to unravel NF-kB control in *H. pylori* infection. Further, a number of evaluated E3 ubiquitin ligases from siRNA screens will be functionally further assessed by a range of established biochemical and cellular approaches regarding their contribution to *H. pylori*-induced NF-kB activity. Finally, molecular traits of NF-kB signal transmission identified in infected gastric cancer cell lines will be investigated in regard to their *in vivo* relevance in experimental infection in mice and paraffin embedded human gastric tissue samples from patient biopsies.

Projektleitung: Prof. Dr. Michael Naumann
Förderer: Deutsche Forschungsgemeinschaft (DFG) - 01.01.2018 - 31.12.2021

Plasticity and cell-type specific functions of OTUB1 in infection

Deubiquitinating enzymes (DUBs) are critical regulators of immune responses and A05 aims to decipher cellular and molecular functions of the DUBs CYLD, A20 and OTUB1 in infectious and autoimmune disorders. Within the 1st funding period, A05 defined that CYLD impairs protective immune responses in listeriosis by inhibiting STAT3-dependent fibrin production in hepatocytes. The 2nd period originated, that CYLD (1) deubiquitinates RIPK2 and inhibits NOD2/RIPK2-mediated autophagy, ROS and NO production in macrophages, and (2) suppresses NF- B-dependent activation in DCs. In contrast, B cell-expressed A20 is essential to prevent spontaneous autoimmunity, whereas DC-specific A20 is required to prevent lethality upon low-dose LPS challenge. In support of a cell type-specific function of DUBs, A05 illustrated that A20 diminishes primary CD8^{+} T cell responses in listeriosis but augments secondary CD8^{+} T cell responses by preventing CD95- and TNF-mediated apoptosis and necroptosis of pathogen-specific memory T cells. Importantly, A05 has established a novel conditional OTUB1 mouse strain and has identified that OTUB1 regulates (1) JAK-dependent cytokine receptor signaling in T cells and (2) TLR/MyD88 -mediated NF- B activation in DCs. In T cells, A05 identified that OTUB1 interacts with and stabilizes SOCS1, which suppresses JAK/STAT signaling. In DCs, OTUB1 is required for Toxoplasma-induced TLR11/12-MyD88-dependent NF- B activation and protective IL-12 production. In the 3rd funding period, A05 will finalize its work on T cell-specific OTUB1 in EAE and DC-specific OTUB1 in toxoplasmosis. In collaboration with other projects of CRC854, A05 will extend its studies to the role of OTUB1 in (1) T cells, (2) DCs, (3) macrophages/granulocytes and (4) hepatocytes in the murine model of listeriosis. Preliminary data already show that the plasticity of the function of OTUB1 is determined by the underlying disease and additionally support our concept of a cell type-specific function OTUB. In fact in listeriosis, OTUB1 (1) prevents cell death of hepatocytes, (2) inhibits cytokine production of DC and (3) is required for T-cell- and macrophage-dependent pathogen control. Therefore, the focus of the studies will be to determine the molecular mechanisms of the cell type-specific function and plasticity of OTUB1, i.e. in listeriosis.

Projektleitung: Prof. Dr. Michael Naumann
Förderer: EU - HORIZONT 2020 - 01.10.2016 - 30.09.2020

ZIKAlliance Project 53

In dem weltweiten Verbund erforschen Wissenschaftler unterschiedlicher Fachdisziplinen das ZIKA-Virus, welches hauptsächlich über Mücken übertragen wird und bereits in 73 Ländern auftritt. Die ZIKA-Virus-Infektion ist unter anderem Ursache für eine Fehlentwicklung des Gehirns bei Neugeborenen, der sogenannten Mikrozephalie. Bis heute gibt es weder eine Impfung zur Infektionsprävention noch eine spezifische Therapie zur Behandlung der ZIKA-Virus-Infektion.
Am Institut für Experimentelle Innere Medizin wird in Kooperation mit dem Max-Planck-Institut für Infektionsbiologie in Berlin ein Verfahren entwickelt, welches es ermöglicht, unter Verwendung der CRISPR/Cas9-Technologie Wirtszellfaktoren zu identifizieren, die für eine ZIKA-Virus-Infektion essentiell sind. Für eine Infektion relevante Wirtszellfaktoren stellen potenzielle Zielstrukturen für eine therapeutische Intervention dar. Die Entwicklung neuer, effizienter Therapieansätze erfordert insbesondere ein fundiertes Verständnis der Regulation und Funktion von Genen während der Infektion. Ziel ist es, Substanzen zu identifizieren, die die Funktion dieser Zielstrukturen spezifisch inhibieren und so die Infektion unterbinden, um neue antivirale Wirkstoffe zu ermitteln.

5. VERÖFFENTLICHUNGEN

BEGUTACHTETE ZEITSCHRIFTENAUFSÄTZE

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ABSTRACTS

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